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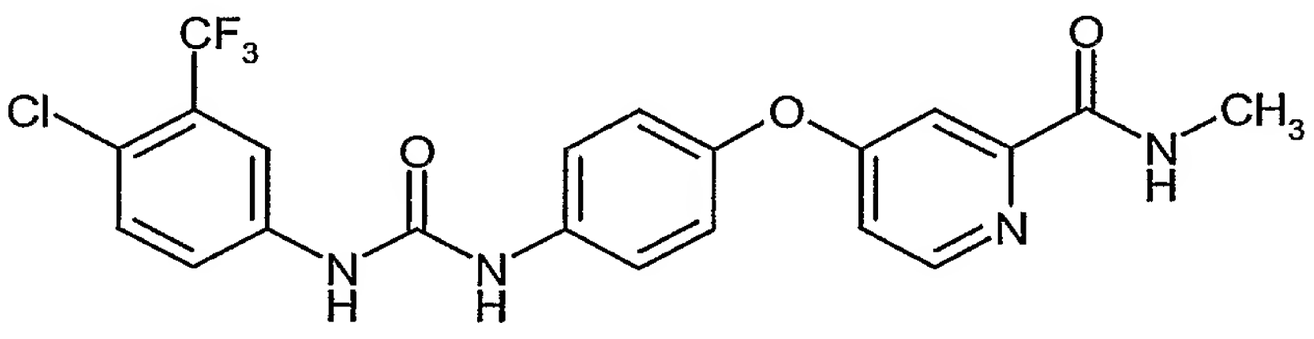
(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING AN OMEGA- CARBOXYARYL SUBSTITUTED DIPHENYL UREA FOR THE TREATMENT OF CANCER



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(57) Abstract: The present invention pertains to a pharmaceutical composition comprising the compound of the formula (I) in a high concentration and at least one pharmaceutically acceptable excipient, the use of the composition for the treatment of hyper-proliferative diseases, such as cancer, either as a sole agent, or in combination with other anti-cancer therapies, and the process for preparing of said composition.

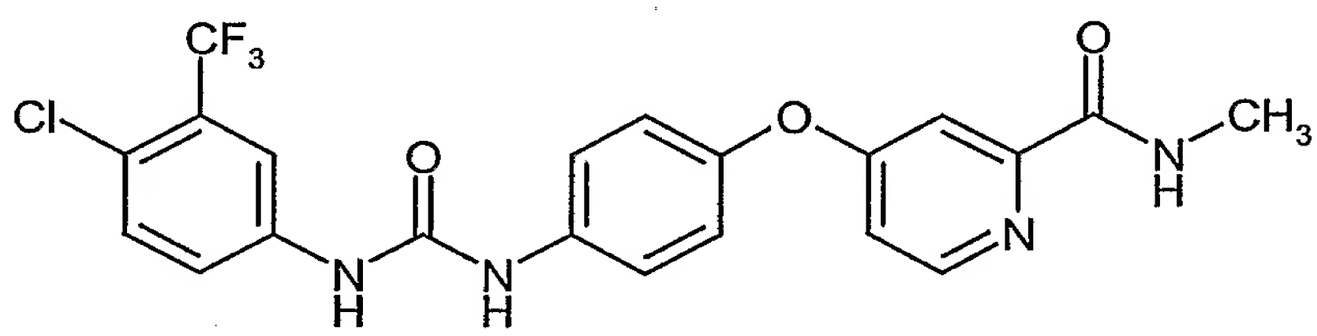
PHARMACEUTICAL COMPOSITION COMPRISING AN OMEGA-CARBOXYARYL SUBSTITUTED DIPHENYL UREA FOR THE TREATMENT OF CANCER

Field of the Invention

This invention relates to novel pharmaceutical compositions and their use for treating hyper-proliferative disorders such as cancer, either as a sole agent or in combination with other anti-cancer therapies and their process for preparing.

Background of the Invention

Diarylureas are a class of serine-threonine kinase inhibitors as well as tyrosine kinase inhibitors known in the art (Smith et al., *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2775-2778, Lowinger et al., *Clin. Cancer Res.* **2000**, *6(suppl.)*, 335, Lyons et al., *Endocr.-Relat. Cancer* **2001**, *8*, 219-225, Lowinger et al., *Curr. Pharm. Design* **2002**, *8*, 99-110). Omega-Carboxyaryl diphenyl ureas are disclosed in WO00/42012 and WO00/41698. In particular, it has been discovered that the diphenyl urea of formula (I),



(I)

also referred as "BAY 43-9006" or 4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)-amino]phenoxy}-*N*-methylpyridine-2-carboxamide, and its pharmaceutically acceptable salts are potent inhibitors of raf, VEGFR-2, p38, and PDGFR kinases. These enzymes are all molecular targets of interest for the treatment of hyper-proliferative diseases, including cancer. Therefore, the compound of formula (I) will be used as medicine for the treatment of the above mentioned diseases.

Despite the progress described in the art with regard to kinase inhibitors, there remains a need for improved medicines for the treatment of cancer. In particular, there remains a need for improved oral pharmaceutical compositions which can be taken in easily and therefore would increase the patient's compliance. The oral pharmaceutical composition has to provide a plasma level of the active agent which is sufficient for an effective therapy. This is dependent on the solubility and the release behavior of the active agent. In the case of a solid pharmaceutical composition the dissolution properties and chemical and mechanical stability are of importance. In order to support a high compliance the oral pharmaceutical composition should not have to be taken in more than three times a day, the less the better, and in the case of a tablet the dimensions of the tablet should

not be too large to allow a good swallowing. The dimensions of a tablet are dependent on the amount of the active agent needed for an effective therapy and the amounts of the excipients. Type and amount of the excipients in combination with the process for preparing are essential for release properties, bioavailability of the compound in mammals, stability and the industrial applicability of the manufacturing process of the pharmaceutical composition.

The objective of the present invention is to provide a pharmaceutical composition comprising the compound of formula (I) which should be applied no more then three times a day in order to achieve an effective plasma level of the compound of formula (I). In the case of a tablet or capsule as oral pharmaceutical composition it should not be too large to provide good swallowing and no more than two should have to be taken in at the same time.

Description of the Invention

The present invention pertains to a pharmaceutical composition comprising the compound of the formula (I) in a high concentration and at least one pharmaceutically acceptable excipient, the use of the composition for the treatment of hyper-proliferative diseases, such as cancer, either as a sole agent, or in combination with other anti-cancer therapies, and the process for preparing of said composition.

Surprisingly the pharmaceutical composition according to the invention has a good bioavailability of the compound of the formula (I), and an effective plasma level is achieved. Furthermore the pharmaceutical composition according to the invention provides a good stability of the compound of the formula (I).

Although the tablets according to the invention are high concentrated on the compound of the formula (I), they surprisingly show good release properties, good bioavailability, high stability and a sufficient hardness. Due to the fact that the pharmaceutical composition according to the invention comprises the compound of the formula (I) in a high concentration dimensions of the composition can be realized which allow a good swallowing of the composition. Therefore the pharmaceutical composition can be taken in easily and supports a high compliance.

The term "the compound of formula (I)", "active agent" or "the compound of this invention" does not only refer to 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methyl amide as depicted in Formula I, but also refers to its polymorphs, solvates, hydrates, pharmaceutically acceptable salts, or a combination thereof.

Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulfuric acid,

phosphoric acid, methanesulphonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid (tosylate salt), 1-naphthalenesulfonic acid, 2-naphthalenesulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid. In addition, pharmaceutically acceptable salts include salts of inorganic bases, such as salts containing alkaline cations (e.g., Li^+ Na^+ or K^+), alkaline earth cations (e.g., Mg^{+2} , Ca^{+2} or Ba^{+2}), the ammonium cation, as well as acid salts of organic bases, including aliphatic and aromatic substituted ammonium, and quaternary ammonium cations, such as those arising from protonation or peralkylation of triethylamine, *N,N*-diethylamine, *N,N*-dicyclohexylamine, lysine, pyridine, *N,N*-dimethylaminopyridine (DMAP), 1,4-diazabiclo[2.2.2]octane (DABCO), 1,5-diazabicyclo[4.3.0]-non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

Solvates for the purposes of the invention are those forms of the compounds where solvent molecules form a complex in the solid state and include, but are not limited to for example ethanol and methanol. Hydrates are a specific form of solvates, where the solvent molecule is water.

Preferably used in the pharmaceutical composition according to the invention is the *p*-toluenesulfonic acid salt of 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methyl amide (tosylate salt of compound (I)). More preferably the *p*-toluenesulfonic acid salt of 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methyl amide exists for at least 80% in the stable polymorph I. Most preferably the *p*-toluenesulfonic acid salt of 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methyl amide exists for at least 80% in the stable polymorph I and in a micronized form.

Micronization can be achieved by standard milling methods, preferably by air chat milling, known to a skilled person. The micronized form can have a mean particle size of from 0.5 to 10 µm, preferably from 1 to 6 µm, more preferably from 1 to 3 µm. The indicated particle size is the mean of the particle size distribution measured by laser diffraction known to a skilled person (measuring device: HELOS, Sympatec).

The process for preparing the *p*-toluenesulfonic acid salt of 4{4-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methyl amide and its stable polymorph I are described in the patent applications EP 04023131.8 and EP 04023130.0.

The inventive pharmaceutical composition comprises the compound of formula (I) in a portion of at least 40%, preferably at least 45%, more preferably at least 50, most preferably at least 55% by weight of the composition.

Preference is given to a pharmaceutical composition comprising the *p*-toluenesulfonic acid salt of 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methyl amide in a portion of at least 55%, preferably at least 62%, more preferably at least 69%, most preferably at least 75% by weight of the composition.

The total amount of the active ingredient (compound of Formula I) to be administered preferably via the oral route using the pharmaceutical composition of the present invention will generally range from about 0.1 mg/kg to about 50 mg/kg body weight per day. Based upon standard laboratory techniques known to evaluate compounds useful for the treatment of hyper-proliferative disorders, by standard toxicity tests and by standard pharmacological assays for the determination of treatment of the conditions identified above in mammals, and by comparison of these results with the results of known medicaments that are used to treat these conditions, the effective dosage of the pharmaceutical compositions of this invention can readily be determined by those skilled in the art. The amount of the administered active ingredient can vary widely according to such considerations as the particular compound and dosage unit employed, the mode and time of administration, the period of treatment, the age, sex, and general condition of the patient treated, the nature and extent of the condition treated, the rate of drug metabolism and excretion, the potential drug combinations and drug-drug interactions, and the like.

Preference is given to an amount of the compound of formula (I) in the pharmaceutical composition from 20 to 2000 mg, preferably from 40 to 800 mg, more preferably from 50 to 600 mg.

Particular preference is given to an amount of *p*-toluenesulfonic acid salt of 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methyl amide in the pharmaceutical composition from 27 to 2740 mg, preferably from 54 to 1096, more preferably from 68 to 822 mg.

The pharmaceutical composition according to the invention is administered one or more, preferably up to three, more preferably up to two times per day. Preference is given to an administration via the oral route. With each administration the number of tablets or capsules taken in at the same time should not exceed two.

Nevertheless, it may in some cases be advantageous to deviate from the amounts specified, depending on body weight, individual behavior toward the active ingredient, type of preparation and time or interval over which the administration is effected. For instance, less than the aforementioned minimum amounts may be sufficient in some cases, while the upper limit specified has to be exceeded in other cases. In the case of administration of relatively large amounts, it may be advisable to divide these into several individual doses over the day.

This pharmaceutical composition will be utilized to achieve the desired pharmacological effect by pereferably oral administration to a patient in need thereof, and will have advantageous properties in terms of drug release, bioavailability, and/or compliance in mammals. A patient, for the purpose of this invention, is a mammal, including a human, in need of treatment for the particular condition or disease.

The pharmaceutical composition comprises suitable administration forms which deliver the compound of the invention in a rapid manner, for example tablets (uncoated or coated tablets), tablets which disintegrate rapidly in the oral cavity or capsules optionally filled with granules (for example hard or soft gelatin capsules), sugar-coated tablets, powders, sachets, granules, pellets, dragées, chewable tablets, dispersible tables, troches and lozenges.

Preference is given to tablets, granules, capsules optionally filled with granules, pellets, dragées, chewable tablets, dispersible tables, troches and lozenges. More preferably the application forms are tablets, granules and capsules optionally filled with granules. Most preferably the application form is a tablet.

The tablet according to the invention shows for example a hardness of more than 80 N, preferably more than or equal to 100 N.

The pharmaceutical composition according to the invention preferably a tablet or a capsule has dimensions which allows good swallowing. Good swallowing depends also on the used format. The longest dimension for example of an oval tablet or capsule is less than or equal to 25 mm. For example a round tablet should have a diameter less than or equal to 13 mm.

The pharmaceutical composition according to the invention shows good release properties. Furthermore preference is given to administration forms wherein the compound of the invention is delivered in a rapid manner also known as "immediate release" administration form. According to the present invention immediate release administration forms having a Q-value (30 minutes) of 75% due to USP-release method with device 2 (paddle, 75 rpm, in 0.1M HCl + 1% sodium dodecylsulfate).

The pharmaceutical composition according to the invention is stable for more than 18 months.

A pharmaceutically acceptable excipient is any excipient which is relatively non-toxic and innocuous to a patient at concentrations consistent with effective activity of the active ingredient so that any side effects ascribable to the excipient do not vitiate the beneficial effects of the active ingredient.

Pharmaceutically acceptable excipients according to the invention are for example disintegrants, binders, lubricants, fillers, plasticizers, surfactants and wetting agents, film-forming agents and coating materials, and coloring agents for example pigments.

Disintegrants include, but are not limited to croscarmellose sodium, crospovidone, alginic acid, , carboxymethylcellulose calcium, carboxymethylcellulose sodium, microcrystalline cellulose, hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, polacrillin potassium, cross-linked polyvinylpyrrolidone, sodium alginate, sodium starch glycollate, partially hydrolysed starch, sodium carboxymethyl starch and starch. Preference is given to croscarmellose sodium and/or cross-linked polyvinylpyrrolidone, more preference is given to croscarmellose sodium.

The amount of the disintegrant contained in the pharmaceutical composition of can be from 0 to 15%, preferably from 5 to 12% by the total weight of the composition.

Binders include, but are not limited to hydroxypropyl cellulose, hypromellose (hydroxypropyl methylcellulose, HPMC), microcrystalline cellulose, acacia, alginic acid, carboxymethylcellulose, ethylcellulose, methylcellulose, hydroxaethylcellulose, ethylhydroxyethylcellulose, polyvinyl alcohol, polyacrylates, carboxymethylcellulose calcium, carboxymethylcellulose sodium, compressible sugar, ethylcellulose, gelatin, liquid glucose, methylcellulose, polyvinyl pyrrolidone and pregelatinized starch. Preference is given to a hydrophilic binder which are soluble in the granulation liquid, more preference is given to hypromellose (hydroxypropyl methylcellulose, HPMC) and/or polyvinylpyrrolidone, most preference is given to hypromellose.

The amount of the binder contained in the pharmaceutical composition of can be from 0 to 15%, preferably from 0.5 to 8% by the total weight of the composition.

Lubricants include, but are not limited to calcium stearate, magnesium stearate, mineral oil, stearic acid, fumaric acid, sodium stearylfumarate, zinc stearate and polyethyleneglycol. Preference is given to magnesium stearate.

The amount of the lubricant contained in the pharmaceutical composition of can be from 0 to 2%, preferably from 0.2 to 0.8% by the total weight of the composition.

Fillers include, but are not limited to dibasic calcium phosphate, kaolin, lactose, mannitol, microcrystalline cellulose, silicated microcrystalline cellulose, dicalcium phosphate, tricalcium phosphate, magnesium trisilicate, mannitol, maltitol, sorbitol, xylitol, lactose for example the anhydrous form or the hydrate form such as the monohydrate form, dextrose, maltose, saccharose, glucose, fructose or maltodextrine, powdered cellulose, precipitated calcium carbonate, sodium carbonate, sodium

phosphate and starch. Preference is given to microcrystalline cellulose, mannitol, lactose and/or dicalcium phosphate, more preference is given to microcrystalline cellulose.

The amount of the filler contained in the pharmaceutical composition of can be from 0 to 60%, preferably from 3 to 20 % by the total weight of the composition.

Surfactants and Wetting agents include, but are not limited to heptadecaethylene oxycetanol, lecithins, sorbitol monooleate, polyoxyethylene sorbitol monooleate, polyoxyethylene stearate, polyoxyethylen sorbitan monolaurate, benzalkonium chloride, nonoxynol 10, oxtoxynol 9, polysorbates for example 20, 40, 60 or 80, sorbitan mono-palmitate, sodium salts of fatty alcohol-sulaftes such as sodium lauryl sulfate, sodium dodecylsulfate, sodium salts of sulfosuccinates such as sodium dioctylsulfosuccinate, partially esters of fatty acids with alcohols such as glycerine monostearate, partially esters of fatty acids with sorbitans such as sorbitan monolaurate, partially esters of fatty acids with polyhydroxyethylene sorbitans such as polyethyleneglycol sorbitan monolaurate, -monostearate or -monooleate, ethers of fatty alcohols with polyhydroxyethylene, esters of fatty acids with polyhydroxyethylene, copolymers of ethylenoxide and propylenoxide (Pluronic®) and ethoxylated triglycerides. Preference is given to sodium lauryl sulfate.

The amount of the surfactant contained in the pharmaceutical composition of can be from 0 to 5 %, preferably from 0.1 to 2 % by the total weight of the composition.

Film-forming agents and coating materials include, but are not limited to liquid glucose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose (hypromellose, HPMC), methylcellulose, ethylcellulose, cellulose acetate phthalate, shellac, polyvinylpyrrolidone, copolymers of vinylpyrrolidone and vinylacetate such as Kollidon® VA64 BASF, copolymers of acrylic- and/or methacrylic acid esters with trimethylammoniummethylacrylate, copolymers of dimethylaminomethacrylic acid and neutral methacrylic acid esters, polymers of methacrylic acid or methacrylic acid esters, copolymers of acrylic acid ethylester and methacrylic acid methyl ester, and copolymers of acrylic acid and acrylic acid methylester. Preference is given to hydroxypropyl methylcellulose (hypromellose, HPMC) as film-forming agent.

Plasticizers include, but are not limited to polyethylene glycol, diethyl phthalate and glycerol. Preference is given to polyethylene glycol.

Coloring agents include, but are not limited to pigments, inorganic pigments, FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel, ferric oxide red, ferric oxide yellow and titanium dioxide. Preference is given to ferric oxide red, ferric oxide yellow and titanium dioxide.

Further commonly used pharmaceutical exipients which can be used as appropriate to formulate the composition for its intended route of administration include, but is not limited to: Acidifying agents for example acetic acid, citric acid, fumaric acid, hydrochloric acid and nitric acid; alkalizing agents for example ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium hydroxide, triethanolamine and trolamine; adsorbents for example powdered cellulose and activated charcoal; stabilizers and antioxidants for example ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorus acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate and sodium metabisulfite; other binding materials for example block polymers, natural and synthetic rubber, polyacrylates, polyurethanes, silicones, polysiloxanes and styrene-butadiene copolymers; buffering agents for examples potassium metaphosphate, dipotassium phosphate, sodium acetate, sodium citrate anhydrous and sodium citrate hydrates; encapsulating agents for example gelatin, starch and cellulose derivates); flavorants, masking agents and odors for example anise oil, cinnamon oil, cocoa, menthol, orange oil, peppermint oil and vanillin; humectants for example glycerol, propylene glycol and sorbitol; sweeteners for example aspartame, dextrose, glycerol, mannitol, propylene glycol, saccharin sodium, sorbitol and sucrose; anti-adherents for example magnesium stearate and talc; direct compression excipients for example dibasic calcium phosphate, lactose and microcrystalline cellulose; tablet polishing agents for example carnauba wax and white wax.

Preference is given to a pharmaceutical composition comprising the compound of the formula (I) in a portion of at least 40%, a filler in a portion of from 0 to 60 %, a disintegrant in a portion of from 0 to 15 %, a binder in a portion of from 0 to 15 %, a lubricant in a portion of from 0 to 2 % and a surfactant in a portion of from 0 to 5 % by weight of the composition.

Also preference is given to a pharmaceutical composition comprising the p-toluenesulfonic acid salt of 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methyl amide in a portion of at least 55%, microcrystalline cellulose as a filler in a portion of from 0 to 60 %, croscarmellose sodium as a disintegrant in a portion of from 0 to 15 %, hypromellose as a binder in a portion of from 0 to 15 %, magnesium stearate as a lubricant in a portion of from 0 to 2 % and sodium lauryl sulfate as a surfactant in a portion of from 0 to 5 % by weight of the composition.

Particular preference is given to a pharmaceutical composition comprising the compound of the formula (I) in a portion of at least 55%, a filler in a portion of from 3 to 20 %, a disintegrant in a portion of from 5 to 12 %, a binder in a portion of from 0.5 to 8 %, a lubricant in a portion of from 0.2 to 0.8 % and a surfactant in a portion of from 0.1 to 2 % by weight of the composition.

Also particular preference is given to a pharmaceutical composition comprising the *p*-toluene-sulfonic acid salt of 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methyl amide in a portion of at least 75%, microcrystalline cellulose as a filler in a portion of from 3 to 20 %, croscarmellose sodium as a disintegrant in a portion of from 5 to 12 %, hypromellose as a binder in a portion of from 0.5 to 8 %, magnesium stearate as a lubricant in a portion of from 0.2 to 8 % and sodium lauryl sulfate as a surfactant in a portion of from 0.1 to 2 % by weight of the composition.

The pharmaceutical composition according to the invention comprising water in an amount of less than or equal to 6 %, preferably less than or equal to 3 %, more preferably less than or equal to 1.5 % by weight of the composition. The water content of the composition is determined by the Karl-Fischer method which is known to a skilled person.

Process for manufacturing

The present invention also relates to a process for the manufacturing of a solid and oral pharmaceutical composition according to the invention, wherein the compound of formula (I) is blended with at least one pharmaceutically acceptable excipient.

Preference is given to a process for the manufacturing of a solid and oral pharmaceutical composition according to the invention, wherein

a) the compound of formula (I) and at least one pharmaceutically acceptable excipient are wet granulated,

b) the granulate is blended with the lubricant and optionally with one or more further pharmaceutically acceptable excipient,

c) the post blend granulate is subdivided into single units ,

d) and the product of step c) is optionally coated with one or more further pharmaceutically acceptable excipients.

Step a: Wet granulation

The compound of formula (I), the filler, preferably microcrystalline cellulose, the binder, preferably hypromellose, the wetting agent, preferably sodium lauryl sulfate and optionally the disintegrant, preferably croscarmellose sodium are granulated in the granulation liquid in terms of a wet granulation. The granulation process is finished when the granulate achieves a „snow ball like consistency“. The wet granulation mass is optionally sized and then dried in a suitable device

for example in a fluidized bed dryer at an inlet air temperature at a range from 50 to 120 °C, preferably from 80 to 100 °C until a residual moisture of less then or equal to 3 % preferrably then or equal to 1.5 % (loss on drying) is reached. The dry granules are optionally sived for example using a sieve size from 1 to 2 mm.

The wet granulation process can be carried out in a high-shear mixer or in a fluidized bed granulator, preferably in a high-shear mixer for wet granulation. The compound of formula (I) can be initially charged as solid in the receiver or is dissolved and/or suspended in the granulation liquid.

Preference is given to a wet granulation process wherein the wetting agent is first dissolved in the granulation liquid and then the blend comprising the compound of formula (I), the filler, the binder and a portion of the disintegrant is added. The blend is mixed before granulation for 1 to 10 minutes, preferably for 1 to 5 minutes.

Alternatively the wetting agent can be added to the dry blend and/or the binder can be dissolved and/or suspended in the granulation liquid.

In the wet granulation process the amount of the granulation liquid is preferably from 40 to 70 %, more preferably from 50 to 60 % by weight of the dry powder blend.

Preferably the compound of formula (I) is used in the crystalline form, more preferably in a micronized form. The micronized form can have a mean particle size of from 0.5 to 10 μm, preferably from 1 to 6 μm, more preferably from 1 to 3 μm.

The wet granulation mass is preferably sized through a rasp from 2 to 8 mm, preferably from 4 to 6 mm.

Solvents such as granulation liquids and film-coating liquids include, but are not limited to ethanol, acetone, glycerol, isopropanol, purified water and mixtures thereof. Preferably the granulation liquids are purified water, ethanol, acetone or mixtures thereof, more preferably purified water.

Preference is given to a process for the manufacturing of a solid and oral pharmaceutical composition according to the invention, wherein the disintegrant is partly used in the granulation process described under a) and the blending process described under b). More preferably an amount of the disintegrant from 3 to 6 % by the total weight of the composition is used in step a) and the remaining is used in step b).

Step b: Blending

The granulate is blended with the lubricant, preferably magnesium stearate and with the remaining disintegrant, preferably croscarmellose sodium, using a suitable device for example a tumbler blender for from 5 to 10 minutes.

Step c: Subdividing/Tablet compression

The blend is subdivided into single units and further processed to the desired administration form known to the person skilled in the art for example filling into sachets or capsules. Optionally one or more further pharmaceutically acceptable excipients are added. Preferably the blend is subdivided into single units and compressed to tablets using for example a standard rotary tablet press at typical tabletting speeds of 25,000 - 250,000 tablets / hour.

Step d: Film-coating

The product of step c) is coated with one or more further pharmaceutically acceptable excipients.

Preference is given to a process for the manufacturing of a solid and oral pharmaceutical composition according to the invention, wherein the one or more further pharmaceutically acceptable excipients is selected from the group of plasticizer, film-forming agents and colorants. The plasticizer, preferably polyethylene glycol, the film-forming agent, preferably hypromellose and the colorants, preferably ferric oxide red and/or yellow, are combined with film-coating liquids, preferably purified water to result in a homogeneous coating suspension which is brought up to, preferably sprayed on the product of step c), preferably on the tablets in a suitable coating device for example a perforated drum coater. Other pigments or water soluble dyes or combinations thereof can be used to modify the color of the coating.

Alternative methods for manufacture of a solid oral pharmaceutical composition according to the invention are:

- The compound of formula (I) and at least one pharmaceutically acceptable excipient are blended without granulation and directly compressed to tablets or filled into capsules or sachets. Further excipients may be utilized to result in the formulation. Optionally, the product can be coated with one or more further pharmaceutically acceptable excipients.

The compound of formula (I) alone or the compound of formula (I) and at least one pharmaceutically acceptable excipient are treated by a dry granulation method and then compressed to tablets or filled into capsules or sachets. Further excipients may be utilized in the formulation.

Optionally, the product can be coated with one or more further pharmaceutically acceptable excipients.

Method of treating hyper-proliferative disorders

The present invention also relates to a method for using the pharmaceutical composition according to the invention to treat mammalian hyper-proliferative disorders, including cancer. This method comprises administering the pharmaceutical composition preferably via the oral route to a mammal in need thereof, including a human, an amount which is effective to treat the disorder. The term "hyper-proliferative disorders" and/or "cancer" not only refers to solid tumors, such as cancers of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid and their distant metastases, but also includes lymphomas, sarcomas, and leukemias.

Examples of breast cancer include, but are not limited to invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma *in situ*, and lobular carcinoma in situ.

Examples of cancers of the respiratory tract include, but are not limited to small-cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma.

Examples of brain cancers include, but are not limited to brain stem and hypophtalmic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumor.

Tumors of the male reproductive organs include, but are not limited to prostate and testicular cancer. Tumors of the female reproductive organs include, but are not limited to endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.

Tumors of the digestive tract include, but are not limited to anal, colon, colorectal, esophageal, gallbladder, gastric, pancreatic, rectal, small intestine, and salivary gland cancers.

Tumors of the urinary tract include, but are not limited to bladder, penile, kidney, renal pelvis, ureter, and urethral cancers.

Eye cancers include, but are not limited to intraocular melanoma and retinoblastoma.

Examples of liver cancers include, but are not limited to hepatocellular carcinoma (liver cell carcinomas with or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma.

Skin cancers include, but are not limited to squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer.

Head-and-neck cancers include, but are not limited to laryngeal / hypopharyngeal / nasopharyngeal / oropharyngeal cancer, and lip and oral cavity cancer.

Lymphomas include, but are not limited to AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Hodgkin's disease, and lymphoma of the central nervous system.

Sarcomas include, but are not limited to sarcoma of the soft tissue, fibrosarcoma, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma.

Leukemias include, but are not limited to acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

These disorders have been well characterized in humans, but also exist with a similar etiology in other mammals, and can be treated by administering the pharmaceutical compositions of the present invention. A patient, for the purpose of this invention, is a mammal, including a human, in need of treatment for the particular condition or disease. Combination therapy

The pharmaceutical compositions of this invention can be administered as the sole agent or in combination with one or more other therapies where the combination causes no unacceptable adverse effects. For example, they can be combined with cytotoxic agents, signal transduction inhibitors, or with other anti-cancer agents or therapies, as well as with admixtures and combinations thereof.

In one embodiment, the pharmaceutical compositions of the present invention can be combined with cytotoxic anti-cancer agents. Examples of such agents can be found in the 11th Edition of the Merck Index (1996). These agents include, by no way of limitation, asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, and vindesine.

Other cytotoxic drugs suitable for use with the pharmaceutical compositions of the invention include, but are not limited to, those compounds acknowledged to be used in the treatment of neoplastic diseases in Goodman and Gilman's The Pharmacological Basis of Therapeutics (Ninth Edition, 1996, McGraw-Hill). These agents include, by no way of limitation, aminoglutethimide, L-asparaginase,

azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2', 2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyladenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel, pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, and vinorelbine.

Other cytotoxic anti-cancer agents suitable for use in combination with the compositions of the invention also include newly discovered cytotoxic principles such as oxaliplatin, gemcitabine, capecitabine, epothilone and its natural or synthetic derivatives, temozolomide (Quinn et al., J. Clin. Oncology 2003, 21(4), 646-651), tositumomab (Bexxar), trabedectin (Vidal et al., Proceedings of the American Society for Clinical Oncology 2004, 23, abstract 3181), and the inhibitors of the kinesin spindle protein Eg5 (Wood et al., Curr. Opin. Pharmacol. 2001, 1, 370-377).

In another embodiment, the pharmaceutical compositions of the present invention can be combined with other signal transduction inhibitors. Of particular interest are signal transduction inhibitors which target the EGFR family, such as EGFR, HER-2, and HER-4 (Raymond et al., Drugs 2000, 60 (Suppl.1), 15-23; Harari et al., Oncogene 2000, 19 (53), 6102-6114), and their respective ligands. Examples of such agents include, by no way of limitation, antibody therapies such as Herceptin (trastuzumab), Erbitux (cetuximab), and pertuzumab. Examples of such therapies also include, by no way of limitation, small-molecule kinase inhibitors such as ZD-1839 / Iressa (Baselga et al., Drugs 2000, 60 (Suppl. 1), 33-40), OSI-774 / Tarceva (Pollack et al. J. Pharm. Exp. Ther. 1999, 291(2), 739-748), CI-1033 (Bridges, Curr. Med. Chem. 1999, 6, 825-843), GW-2016 (Lackey et al., 92nd AACR Meeting, New Orleans, March 24-28, 2001, abstract 4582), CP-724,714 (Jani et al., Proceedings of the American Society for Clinical Oncology 2004, 23, abstract 3122), HKI-272 (Rabindran et al., Cancer Res. 2004, 64, 3958-3965), and EKB-569 (Greenberger et al., 11th NCI-EORTC-AACR Symposium on New Drugs in Cancer Therapy, Amsterdam, November 7-10, 2000, abstract 388).

In another embodiment, the pharmaceutical compositions of the present invention can be combined with other signal transduction inhibitors targeting receptor kinases of the split-kinase domain families (VEGFR, FGFR, PDGFR, flt-3, c-kit, c-fms, and the like), and their respective ligands. These agents include, by no way of limitation, antibodies such as Avastin (bevacizumab). These agents also include, by no way of limitation, small-molecule inhibitors such as STI-571 / Gleevec (Zvelebil, Curr. Opin. Oncol., Endocr. Metab. Invest. Drugs 2000, 2(1), 74-82), PTK-787 (Wood et al., Cancer Res. 2000, 60(8), 2178-2189), SU-11248 (Demetri et al., Proceedings of the American Society for Clinical Oncology 2004, 23, abstract 3001), ZD-6474 (Hennequin et al., 92nd AACR Meeting, New Orleans, March 24-28, 2001, abstract 3152), AG-13736 (Herbst et al., Clin. Cancer Res. 2003, 9, 16 (suppl 1),

abstract C253), KRN-951 (Taguchi et al., 95th AACR Meeting, Orlando, FL, 2004, abstract 2575), CP-547,632 (Beebe et al., Cancer Res. 2003, 63, 7301-7309), CP-673,451 (Roberts et al., Proceedings of the American Association of Cancer Research 2004, 45, abstract 3989), CHIR-258 (Lee et al., Proceedings of the American Association of Cancer Research 2004, 45, abstract 2130), MLN-518 (Shen et al., Blood 2003, 102, 11, abstract 476), and AZD-2171 (Hennequin et al., Proceedings of the American Association of Cancer Research 2004, 45, abstract 4539).

In another embodiment, the pharmaceutical compositions of the present invention can be combined with inhibitors of the Raf/MEK/ERK transduction pathway (Avruch et al., Recent Prog. Horm. Res. 2001, 56, 127-155), or the PKB (akt) pathway (Lawlor et al., J. Cell Sci. 2001, 114, 2903-2910). These include, by no way of limitation, PD-325901 (Sebolt-Leopold et al., Proceedings of the American Association of Cancer Research 2004, 45, abstract 4003), and ARRY-142886 (Wallace et al., Proceedings of the American Association of Cancer Research 2004, 45, abstract 3891).

In another embodiment, the pharmaceutical compositions of the present invention can be combined with inhibitors of histone deacetylase. Examples of such agents include, by no way of limitation, suberoylanilide hydroxamic acid (SAHA), LAQ-824 (Ottmann et al., Proceedings of the American Society for Clinical Oncology 2004, 23, abstract 3024), LBH-589 (Beck et al., Proceedings of the American Society for Clinical Oncology 2004, 23, abstract 3025), MS-275 (Ryan et al., Proceedings of the American Association of Cancer Research 2004, 45, abstract 2452), and FR-901228 (Piekarz et al., Proceedings of the American Society for Clinical Oncology 2004, 23, abstract 3028).

In another embodiment, the pharmaceutical compositions of the present invention can be combined with other anti-cancer agents such as proteasome inhibitors, and m-TOR inhibitors. These include, by no way of limitation, bortezomib (Mackay et al., Proceedings of the American Society for Clinical Oncology 2004, 23, Abstract 3109), and CCI-779 (Wu et al., Proceedings of the American Association of Cancer Research 2004, 45, abstract 3849).

Generally, the use of cytotoxic and/or cytostatic anti-cancer agents in combination with the pharmaceutical compositions of the present invention will serve to:

(1) yield better efficacy in reducing the growth of a tumor or even eliminate the tumor as compared to administration of either agent alone,

(2) provide for the administration of lesser amounts of the administered agents,

(3) provide for a chemotherapeutic treatment protocol that is well tolerated in the patient with fewer deleterious pharmacological complications than observed with single agent chemotherapies and certain other combined therapies,

(4) provide for treating a broader spectrum of different cancer types in mammals, especially humans,

(5) provide for a higher response rate among treated patients,

(6) provide for a longer survival time among treated patients compared to standard chemotherapy treatments,

(7) provide a longer time for tumor progression, and/or

(8) yield efficacy and tolerability results at least as good as those of the agents used alone, compared to known instances where other cancer agent combinations produce antagonistic effects. It is believed that one skilled in the art, using the preceding information and information available in the art, can utilize the present invention to its fullest extent.

It should be apparent to one of ordinary skill in the art that changes and modifications can be made to this invention without departing from the spirit or scope of the invention as it is set forth herein.

All publications, applications and patents cited above and below are incorporated herein by reference.

The weight data are, unless stated otherwise, percentages by weight and parts are parts by weight.

Examples:

Example 1: Immediate release tablet containing the tosylate salt of compound of formula (I) and optionally subsequent film-coating

1.1 Composition of tablets containing the *p*-toluenesulfonic acid salt of 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methyl amide (tosylate salt of compound (I))

Composition [mg/tablet]	Tablet A 50 mg	Tablet B 200 mg	Tablet C 200 mg	Tablet D 400 mg
Tablet core:	step a), b)	step a), b), c) ii	Step a), b) c) i	Step a), b) c) i
Tosylate salt of compound (I) micronized	68.5 mg	274.0 mg	274.0 mg	548.0 mg
Microcrystalline cellulose	4.0 mg	16.0 mg	16.0 mg	32.0 mg
Croscarmellose sodium	9.1 mg	36.4 mg	36.4 mg	72.8 mg
Hypromellose (5 cP)	2.55 mg	10.2 mg	10.2 mg	20.4 mg
Magnesium stearate	0.425 mg	1.7 mg	2.55 mg[#1] (1.70 - 2.55 mg)	5.10 mg
Sodium lauryl sulfate	0.425 mg	1.7 mg	1.7 mg	3.4 mg
Weight	**85.0 mg**	**340.0 mg**	**340.85 mg** (340.0 - 340.85 mg)	**681.70 mg**
Film-coating:				
Opadry Red YS2-15531[#3]	-----	10.0 mg	--[#2]--	--[#2]--
Hypromellose (15 cP)	-----	-----	6.00 mg (4.8 – 7.2 mg)	9.0 mg (7.2-10.8 mg)
Macrogol 3350 (polyethylene gycol)	-----	-----	2.00 mg (1.6 – 2.4 mg)	3.0 mg (2.4-3.6 mg)
Titanium dioxide	-----	-----	1.73 mg (1.384 – 2.076 mg)	1.6 mg (1.28-1.92 mg)
Ferric oxide (red)	-----	-----	0.27 mg (0.216 – 0.324 mg)	-----
Ferric oxide (yellow)	-----	-----	-----	1.4 mg (1.12-1.68 mg)
Weight of film coat	-----	10.0 mg	10.0 mg (8.0 – 12.0 mg)	15.0 mg (12.0 – 18.0 mg)
Total tablet weight	**85.0 mg**	**350.0 mg**	**350.85 mg** (348 – 352.85 mg)	**696.7 mg** (348.0-352.85 mg)
Tablet format	**Round**	**round**	**round**	**oval**
Dimensions of the tablet	**diameter: 6 mm**	**diameter: 10 mm, height: 4.5 (±0.3) mm**	**diameter: 10 mm, height: 4.5 (±0.3) mm**	**length: 18 mm, width: 8 mm**

[#1] Range for Mg stearate may apply according to manufacturing conditions

[#2] Range for film coat may apply according to manufacturing conditions Fixed ratio of coating components 60 % (hypromellose) – 20 % (polyethylene glycol) – 17.3 % (titanium dioxide) – 2.7 % ferric oxide

[#3] Opadry Red YS-15531 ready to use commercial coating system.

1.2 Process for manufacturing

Step a) Granulation

4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methyl amide (tosylate salt of compound (I) micronized, microcrystalline cellulose, croscarmellose sodium, and hypromellose are mixed for 2 minutes in a high shear mixer in order to obtain a powder blend. Sodium lauryl sulfate is dissolved in water. The powder blend is granulated with the solution in a wet granulation process using a high-shear mixer. The granulation process is finished when the granulate achieves a „snow ball like consistency". The wet granulation mass is sized using a 4 mm rasp and then dried in a fluidized bed dryer at an inlet air temperature of 80 - 100 °C until a residual moisture of 0.3 up to 0.7% by weight (loss on drying) is reached. The dry granules are sieved using a 2 mm sieve size.

Step b) Tablet compression

The granulate is blended with magnesium stearate and croscarmellose sodium using a tumbler blender for from 5 to 10 minutes. The blend is subdivided into single units and compressed to tablets using a standard rotary tablet press at typical tabletting speeds of from 25,000 to 250,000 tablets / hour.

Step c) Film-coating

Alternative i:

Hypromellose, polyethylene glycol (Macrogol), titanium dioxide and ferric oxide red are combined with purified water to result in a homogenous coating suspension which is sprayed on the tablets in a perforated drum coater.

Alternative ii:

The commercially available Opadry Red YS-15531 is combined with purified water to result in a homogenous coating suspension which is sprayed on the tablets in a perforated drum coater.

1.3 Properties of the tablets

Tab. 1: Study of release of compound of formula (I) from tablets B and C

Release of the compound of the formula (I) in % by total weight of the composition.

	15 min	30 min	45 min	60 min
Tablet B	94	97	97	97
Tablet C	96	99	99	99

Each value represents the mean of 6 single results. USP apparatus 2, 900 ml 0.1 N HCl + 1% Sodium Lauryl Sulfate, 100 rpm

The tablets have a stability of more than 18 months (real time stability data) and a hardness of more than 100 N.

The water content of the tablets is less then 1.5 % by weight of the composition (determination: Karl-Fischer method)

What is claimed is:

1. A pharmaceutical composition comprising 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methyl amide, its solvates, hydrates, pharmaceutically acceptable salts, or a combination thereof as active agent in a portion of at least 40% by weight of the composition and at least one pharmaceutically acceptable excipient.

2. The pharmaceutical composition of claim 1 comprising the active agent in a portion of at least 55% by weight of the composition.

3. The pharmaceutical composition of any of claims 1 to 2 wherein the active agent is the *p*-toluenesulfonic acid salt of 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methyl amide.

4. The pharmaceutical composition of claim 3 comprising the active agent in a portion of at least 55% by weight of the composition.

5. The pharmaceutical composition of claim 3 comprising the active agent in a portion of at least 75% by weight of the composition.

6. The pharmaceutical composition of any of claims 3 to 5 wherein the *p*-toluenesulfonic acid salt of 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methyl amide exists for at least 80% in the stable polymorph I.

7. The pharmaceutical composition of claim 1 comprising the active agent in a portion of at least 40%, a filler in a portion of from 0 to 60 %, a disintegrant in a portion of from 0 to 15 %, a binder in a portion of from 0 to 15 %, a lubricant in a portion of from 0 to 2 % and a surfactant in a portion of from 0 to 5 % by weight of the composition.

8. The pharmaceutical composition of any of claims 1 to 7 comprising the *p*-toluenesulfonic acid salt of 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methyl amide in a portion of at least 55%, microcrystalline cellulose as a filler in a portion of from 0 to 60 %, croscarmellose sodium as a disintegrant in a portion of from 0 to 15 %, hypromellose as a binder in a portion of from 0 to 15 %, magnesium stearate as a lubricant in a portion of from 0 to 2 % and sodium lauryl sulfate as a surfactant in a portion of from 0 to 5 % by weight of the composition.

9. The pharmaceutical composition of any of claims 1 to 8 for oral administration.

10. The pharmaceutical composition of any of claims 1 to 9 is solid oral dosage form.

11. The pharmaceutical composition of any of claims 1 to 10 is a tablet.

12. The pharmaceutical composition of any of claims 1 to 11 is an immediate release tablet.

13. The pharmaceutical composition of any of claims 1 to 12 wherein the active agent is micronized.

14. The pharmaceutical composition of any of claims 1 to 13 comprising water in an amount of less than or equal to 6 % by weight of the composition.

15. The pharmaceutical composition according to any of claims 1 to 14 in combination with one or more cytotoxic agents, signal transduction inhibitors, or with other anti-cancer agents or therapies, as well as with admixtures and combinations thereof.

16. A process for manufacturing a pharmaceutical composition according to any of claims 1 to 14 wherein the active agent is blended with at least one pharmaceutically acceptable exipient.

17. The process of claim 16 wherein:

a) the active agent and at least one pharmaceutically acceptable excipient are wet granulated,

b) the granulate is blended with the lubricant and optionally with one or more further pharmaceutically acceptable excipient,

c) the post blend granulate is subdivided into single units ,

d) and the product of step c) is optionally coated with one or more further pharmaceutically acceptable excipients.

18. The process of any of claims 16 to 17 wherein the product of step c) is a tablet, capsule or sachet.

19. The process of any of claims 16 to 18 wherein the product of step c) is coated with one or more further pharmaceutically acceptable excipients

20. The process of claim 16 wherein the active agent and at least one pharmaceutically acceptable excipient are blended without granulation and directly compressed to tablets or filled into capsules or sachets.

21. The process of claim 16 wherein the active agent anlone or the active agent and at least one pharmaceutically acceptable excipient are treated by a dry granulation method and then compressed to tablets or filled into capsules or sachets.

22. Method for using the pharmaceutical composition according to any of claims 1 to 15 to treat mammalian hyper-proliferative disorders, including cancer.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/001574

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K9/22 A61K9/36 A61K31/4412 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, PAJ, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/125359 A1 (LYONS JOHN F ET AL) 3 July 2003 (2003-07-03) paragraph [0030] - paragraph [0034] -----	1,2,4,5, 9-12,15, 22
A	WILHELM SCOTT M ET AL: "BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis" CANCER RESEARCH, vol. 64, no. 19, 1 October 2004 (2004-10-01), pages 7099-7109, XP002384320 ISSN: 0008-5472 page 7100, column 1, paragraph 2 -----	1-22

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 June 2006	12/07/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Sindel, U

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/001574

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	AHMAD T ET AL: "Kinase inhibition with BAY 43-9006 in renal cell carcinoma" CLINICAL CANCER RESEARCH, THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, US, vol. 10, no. 18 Pt 2, 19 March 2004 (2004-03-19), pages 6388S-6392S, XP002362669 ISSN: 1078-0432 page 6389S, column 1, paragraph 2	1-22
A	KRAMER BORIS W ET AL: "Use of mitogenic cascade blockers for treatment of C-Raf induced lung adenoma in vivo: CI-1040 strongly reduces growth and improves lung structure." BMC CANCER [ELECTRONIC RESOURCE]. 1 JUN 2004, vol. 4, 1 June 2004 (2004-06-01), page 24, XP002384321 ISSN: 1471-2407 abstract	1-22
A	WO 2005/009367 A (AMBIT BIOSCIENCES CORPORATION; BIGGS III, WILLIAM, H; CARTER, TODD; FA) 3 February 2005 (2005-02-03) paragraph [0015] paragraph [0069] - paragraph [0071]	1-22
A	US 2003/207872 A1 (RIEDL BERND ET AL) 6 November 2003 (2003-11-06) paragraph [0040] - paragraph [0044] paragraph [0185] - paragraph [0186]	1-22

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/001574

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 22 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2006/001574

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2003125359 A1	03-07-2003	NONE	
WO 2005009367 A	03-02-2005	NONE	
US 2003207872 A1	06-11-2003	NONE	